## REMARKS

Claims 1-12, 14, and 16-28 were pending in this application. Accordingly, claims 1-12, 14, and 16-28 are now pending and under examination.

### *Interview Summary*

The Applicants express their gratitude for the personal interview between Examiner K. Horlick, inventor, Dr. Charles Cantor, and Applicants' representative, Catherine Polizzi, on April 14, 2009. The time, consideration, and suggestions by the Examiner are greatly appreciated.

During the interview, the rejections under § 103(a) of all the claims were discussed in view of the references cited by the Examiner in the Office Action dated 12/04/2008, particularly Landegren et al., Michnick et al., and Singer et al. Applicants discussed why there would not have been motivation and/or reasonable expectation of success for combining the cited references. No agreement was reached.

### *35 U.S.C. § 112, second paragraph*

Claims 25-28 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regards as the invention. Applicants respectfully traverse.

The Examiner alleges that claims 25-28 are confusing because it is unclear how a living cell may be "in vivo" or "in vitro."

Applicants respectfully submit that claims 25-28 are clear. Independent claim 1 recites a method for the detection of a target nucleic acid in a living cell, and independent claim 21 recites a kit for the detection of a target nucleic acid molecule in a living cell. A person skilled in the art would understand that the living cell could be present and living in the context of an organism (*e.g.*, in vivo) or that the living cell could be present and living outside the context of an organism, such as in tissue culture (*e.g.*, in vitro).

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claims 25-28 under 35 U.S.C. § 112, second paragraph.

***35 U.S.C. § 103(a)***

*I. Claims 1-3, 5-12, 14, 16-17, 19, and 25-26*

Claims 1-3, 5-12, 14, 16-17, 19, and 25-26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964) and further in view of Singer et al. (U.S. 5,728,527) or van Dongen et al. (U.S. 6,730,474). Applicants respectfully traverse.

The Examiner states that Landegren et al. disclose the use of "proximity probes", wherein when first and second binding portions of first and second probes bind a target molecule, complementary first and second oligonucleotides attached to said first and second binding portions interact via hybridization and are detected. Office Action dated December 4, 2008 at page 7. The Examiner acknowledges that Landegren et al. do not disclose the use of polypeptide fragments which form a complementation complex as the basis for detection. Office Action at page 8. However, the Examiner alleges that one of ordinary skill in the art would have been motivated to substitute polypeptides which together form a complementation complex for the complementary nucleic acids in Landegren et al. because such a complementation complex was disclosed by Michnick et al., and would have merely provided a predictable and reasonably likely successful alternative detection mean to the complementary nucleic acid means of Landegren et al. Office Action at pages 8-9. The Examiner further alleges that a skilled artisan would have been further motivated to carry out the method in living cells in view of Singer et al. and van Dongen et al.

Applicants respectfully disagree. Applicants submit that a person skilled in the art would not have been motivated to substitute the nucleic acid based detection system of Landegren et al. with the split polypeptide complementation system of Michnick et al. and that there was no reasonable likelihood of success in achieving the claimed methods in view of Landegren et al. and Michnick et al.

The claimed methods and kits for detection in the present application provide highly specific, sensitive, and reliable methods for detecting nucleic acids of interest. As discussed in the specification, the

> majority of detection methods have relied on nucleic acid probes to detect a nucleic acid of interest.... Nonetheless, probe-based assays have been hampered in part by difficulties associated with specificity, sensitivity and reliability, and challenges presented by detection of nucleic acids in vivo.

Paragraph [0009]. Further, "[s]everal nucleic acid probe-based methods have been developed for the detection of nucleic acids. Most are designed around the amplification of sectioned targets and/or probes composed of DNA." Paragraph [0011]. The specification notes, however, "these methods are associated with a number of difficulties, including relatively low precision in quantitative measurements, being laborious, expensive, time-consuming, inefficient, and lacking in sensitivity." Paragraph [0012]. The specific, sensitive, and reliable methods of the present application, which provide a unique combination of components which together form a highly effective system, allow the rapid, efficient, and sensitive detection of a target nucleic acid. This is achieved by using a split polypeptide portion that forms an assembled complementation complex only when brought into proximity by nucleic acid probe portions binding to specified sequences on a target nucleic acid.

This detection system is not taught in the prior art. Prior technology such as Landegren et al., which teach a detection system premised upon the interaction of nucleic acid detection component, nucleic acid reactive proximity probes, and their subsequent detection by a secondary step/reaction, is associated with a number of difficulties, as discussed above, such as being laborious and time-consuming as a secondary step/reaction is required. Other technology such as Michnick et al., which teach a method of detecting protein interactions premised upon the assembly of a complementation complex formed when a split enzyme is brought in proximity by protein interactions, has not been used as a means to detect target nucleic acids, let alone the use of nucleic acid probes to enhance the specificity and generality of the technology to detect any target nucleic acid. Based on the multiple layers of complexity associated with the present detection system and the limited predictability regarding the substitution of a protein component for a nucleic acid component in the present detection system, a person skilled in the art would have no reasonable expectation of success in arriving at the claimed invention.

*Landegren et al. and Michnick et al.*

Applicants submit that the claimed invention is strikingly and significantly different, as well as improved, from what is disclosed in the cited references. Applicants further respectfully submit that a person skilled in the art would not have been motivated to substitute the polypeptides of Michnick et al. which together form a complementation complex for the complementary nucleic acids in Landegren et al. to arrive at the claimed invention as: a) neither Landegren et al. nor Michnick et al. lead one skilled in the art to substitute the polypeptide fragments of a split enzyme of Michnick et al. for the complementary nucleic acids in Landegren et al. as the detection system of Landegren et al. is fundamentally premised on the use of nucleic acids as read out for detection of a target molecule, b) one skilled in the art is not motivated to substitute the polypeptide fragments of a split enzyme of Michnick et al. for the complementary nucleic acids in Landegren et al. in view of the general and fundamental differences between proteins and nucleic acid complementation, c) neither Landegren et al. nor Michnick et al. lead one skilled in the art to substitute the polypeptide fragments of a split enzyme of Michnick et al. for the complementary nucleic acids in Landegren et al. as the inventive detection system in Landegren et al. further requires a nucleic acid specific secondary reaction/step to detect a target molecule, d) Landegren et al. would not lead one skilled in the art to use a nucleic acid probe to bind to a nucleic acid target analyte, e) Michnick et al. would not lead one skilled in the art to detect a target nucleic acid analyte, and f) Landegren et al. would not lead one skilled in the art to use the detection system in Landegren et al. in intact cells.

The key and centerpiece methods of Landegren et al. are the use of the interaction of the nucleic acid detection component when in contact to create a secondarily detectable nucleic acid interaction. The inventive and fundamental basis of the system according to Landegren et al. is the use of a *nucleic acid detection component*. There is no teaching or suggestion in Landegren et al. that the methods of detection utilized can be reconstituted using a protein as the reactive functionality of a proximity probe. Further, there is no motivation to substitute the nucleic acid, reactive functionality of the proximity probe in Landegren et al. for polypeptide fragments of a split enzyme of Michnick et al.

The methods of detection in Landegren et al. operate under the principle that the detection component, a nucleic acid reactive functionality of a proximity probe, when brought close by

binding of the analyte interact and the interaction is detected in a secondary reaction/step such as PCR. Landegren et al. expressly state:

> The *analyte acts in a way analogous to a catalyst by bring the reactive probes closer to one another and increasing their ability to interact* through an increase local concentration. The interaction between the couple functionalities results in a detectable signal *in a secondary reaction*."

Paragraph [0006] (emphasis added). In addition, Landegren et al. state that the

> reactive functionality of a proximity-probe is comprised of a nucleic acid coupled to a binding moiety.... the proximity of these target bound nucleic acids is used to *promote various detectable interactions between these nucleic acids*. This nucleic acid interaction is *detected in a secondary step* of the analysis

and, in most cases, the secondary detection involves specific amplification. Paragraph [0011]. (Emphasis added.)

Landegren et al. disclose a detection method based upon the reactive functionality of the nucleic acid proximity-probe being brought in close proximity. In contrast, in Michnick et al., the detection of protein interactions is premised upon reconstitution of enzymatic activity of split polypeptide fragments. To effectuate the secondary detection, the nucleic acid reactive functionality of Landegren et al. requires only interaction on the nucleic acid reactive functionality. In contrast, the protein/protein interactions of Michnick et al. must reconstitute split enzyme catalytic activity and result in a detectable signal.

In determining whether an invention is obvious, the claimed invention as a whole must be considered. M.P.E.P. § 2141.02(I). In determining the differences between the prior art and the claims, the question under 35 USC § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. M.P.E.P. § 2141.02(I). If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teaching of the references are not sufficient to render the claims *prima facia* obvious. M.P.E.P. § 2143.01(VI).

The invention of Landegren et al. is premised upon the use of a nucleic acid detection signal while Michnick et al. is premised upon reconstitution of split enzyme activity. The proposed substitution of the polypeptide fragments of the split enzyme of Michnick et al. with the nucleic acid

detection component, the reactive functionality of the nucleic acid proximity-probe, of Landegren et al. would eviscerate the entire operating principle of Landegren's detection system. As such, Applicants respectfully submit that the obviousness rejection can be withdrawn on this basis.

Second and further to the discussion above, the interaction of the reactive probes in Landegren et al. is detected via a secondary reaction/step. Paragraphs [0006] and [0011].[1] The specific amplification steps to detect the nucleic acid interaction recited in Landegren et al. are specific for nucleic acids. Replacing the nucleic acid proximity-probe with a protein proximity-probe such as those in Michnick et al. would change the underlying principles by which the Landegren et al. invention was based.

As noted above the method of Landegren et al. is further based on detection in a nucleic acid specific secondary reaction/step. In the present invention, there is no necessity for a secondary reaction/step to detect the binding of probes to the analyte. A prior art reference must be considered in it entirety, i.e., as a whole, including portions that would lead away from the claimed invention. M.P.E.P. § 2141.02(VI). If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teaching of the references are not sufficient to render the claims *prima facia* obvious. M.P.E.P. § 2143.01(VI). The invention of Landegren et al. is premised upon the use of nucleic acid specific secondary reactions/steps to detect the proximity of the nucleic acid proximity-probes. Michnick et al. does not utilize or contemplate the use of nucleic acid specific secondary reactions/steps or nucleic acid proximity-probes, but instead is premised upon direct reconstitution of split enzyme activity and production of a detectable signal. Again, there is no suggestion or motivation to modify Landegren et al. as indicated by the Examiner, as the modification of Landegren et al. in view of Michnick et al. changes the underlying principles by which the Landegren et al. invention was based and operates.

Third, although Landegren et al. include nucleic acids amongst lists of potential analytes and binding moieties (Paragraphs [0007] and [0010]) Landegren et al. also state that the method for detecting and/or qualifying one or more analyte(s) in solution (described as an aspect of the

invention) contains the explicit proviso that *the binding moieties and the analyte(s) not all comprise a nucleic acid.* Paragraphs [0017]-[0019]. Thus, the very configuration currently claimed in the instant case is expressly excluded. Further and in accordance with this express exclusion of the configuration claimed in the instant case, the only working example in Landegren et al. directed to the use of nucleic acid binding moiety is to detect a protein analyte. Example 1. This is also consonant with the teaching of Landegren et al. which points to primary purpose and use of the disclosed technology to detect protein targets as indicated by the examples.

A prior art reference must be considered in it entirety, i.e., as a whole, including portions that would lead away from the claimed invention. M.P.E.P. § 2141.02(VI). The proviso in Landegren et al. that the binding moieties and the analyte(s) not all comprise a nucleic acid would lead a person skilled in the art away from the presently claimed invention. There is no suggestion or motivation to modify Landegren et al. as indicated by the Examiner. Therefore, Landegren et al. is distanced even further from the instant invention.

Fourth, in regards to Michnick et al., the molecules of Michnick et al. are designed to detect protein interactions, not to detect a target analyte per se. Col. 3, lines 38-43 and Abstract. The purpose of the molecules and assays of Michnick et al. is to screen for protein interactions of systems attached to the split enzyme, not to detect a target analyte. Applicants note that Example 4 is related to the detection of multiprotein, protein-RNA, protein-DNA or protein-small molecule interactions. Example 4 states at column 29, line 61 – column 30, line 28:

> The utility of PCA is not limited to detecting protein-protein interactions, but can be adapted to *detecting interactions of proteins* with DNA, RNA, or small molecules. In this conception, two proteins are fused to PCA complementary fragments, but the two proteins do not interact with each other. The *interaction must be triggered by a third entity*, which can be any molecule that will simultaneously bind to the two proteins or induce an interaction between the two proteins or induce an interaction between the two proteins by causing a conformational change in one or both of the partners.

(Emphasis added.)

As illustrated above, the purpose of Michnick et al. is to detect interaction of proteins/polypeptide fragments attached to the split enzyme, not to detect a target analyte. As

[1] The amplification assays identified in Landegren et al. include polymerase chain reaction (PCR), strand displacement amplification, NASBA, RNA transcription, and invader assays. Paragraph [0014].

previously stated, a prior art reference must be considered in it entirety, i.e., as a whole. M.P.E.P. § 2141.02(VI). The stated purpose described in Landegren et al., which is directed to detection of a target analyte, and Michnick et al., which is directed to detection of protein interactions, are different. A person skilled in the art would not be motivated to combine Landegren et al. and Michnick et al. as the very objective and purpose of their inventions are to address different scientific questions and problems.

Finally, Landegren et al. is directed to detection of analytes in a homogeneous solution, not in an intact cell in vivo or in vitro. Landegren et al. at paragraph [0006] state that "[t]his invention is char[]acterized by its ability to detect and quantify one or several analytes in *solution in a homogenous* one tube assay with high sensitivity and specificity." (Emphasis added.) There is no suggestion that the methods of Landegren et al. can or should be used in an intact cell or motivation to modify the teaching of Landegren et al. to the subject matter of the present claims. In fact, Landegren et al. expressly state that their methods are to be used in a context other than in intact cells.

Applicants additionally submit that that there was no reasonable likelihood of success in achieving the claimed invention based on the disclosure of Landegren et al. in view of Michnick et al.

The Examiner alleges that the substitution of polypeptides which together form a complementation complex of Michnick et al. for the complementary nucleic acids in the method of Landegren et al. merely provides a predictable and reasonably likely successful alternative detection means to the complementary nucleic acids means of Landegren et al. Office Action at pages 8-9.

Applicants respectfully disagree and submit that even if a person skilled in the art were motivated to substitute the polypeptides of Michnick et al. for the complementary nucleic acids in Landegren et al. (though Applicants respectfully disagree with this premise) there is no predictable, reasonable expectation that the claimed methods for detecting a target nucleic acid molecule would be successful in view of Landegren et al. and Michnick et al. as there is no reasonable expectation of success in replacing the nucleic acid proximity probes and secondary detection of Landegren et al. with a protein complementation system of Michnick et al. or replacing the fused, interacting

protein of Michnick et al. with a fused, interacting nucleic acid.[2] Further, there is no reasonable expectation of success of being able to detect a target analyte in view of the disclosure of Michnick et al. related to the detection of protein interactions.

First, there is no reasonable expectation of success in interchanging the detection system based on nucleic acid proximate probe interactions and secondary detection of Landegren et al. with the protein complementation system in Michnick et al. The principles and properties associated with nucleic acid/nucleic acid interactions and protein/protein interactions are significantly different, such as the requirements for binding and intrinsic properties of proteins and nucleic acids. These fundamental differences between nucleic acids and proteins are particularly problematic in predicting how substituting a nucleic acid component with a protein component will behave in a detection system, particularly the detection system as claimed.

The nucleic acid-based detection system in Landegren et al. requires the detection nucleic acids to interact, but does not require restoration of a catalytic activity. In fact, the method of Landegren et al. requires a nucleic acid specific secondary step/reaction to detect the interaction of the detection nucleic acid proximity probe. In contrast, the methods of Michnick et al. require reassembly of the catalytic activity of the polypeptide fragments of the split enzyme. Michnick et al. expressly state that "[i]t is crucial to understand that these assays will only work if the fused, interacting proteins catalyze the reassembly of the activity." Michnick et al. at column 4, lines 38-40.

Secondly, Applicants submit that prior to the Applicants' disclosure, there was no predictable, reasonable expectation of success for one skilled in the art to reconstitute the catalytic activity of a split enzyme by the use of a nucleic acid probe binding to a nucleic acid target analyte.

Michnick et al. teach that protein complementation and restoration of catalytic activity can occur if the fused, interacting proteins catalyze the assembly. There is no teaching or suggestion in

[2] Applicants note that Michnick et al. do not state where the nucleic acid binding proteins bind on the target nucleic acid, i.e., Michnick et al. do not state that the attached nucleic acid-binding proteins bind to "nearby regions of the target nucleic acid" as indicated by the Examiner at page 8 of the Office Action. Further, Michnick et al. do not disclose detection of "proximate binding site in a target molecule" as indicated by the Examiner at page 8 of the Office Action. Applicants also note that Landegren et al. do not disclose first and second probes binding to "adjacent sites" on a target molecule as stated by the Examiner.

either Landegren et al. or Michnick et al. that a nucleic acid probe by interacting with a nucleic acid analyte can facilitate protein complementation and restore enzyme activity of the detection component. Further, the fundamental differences in proteins and nucleic acids would leave one skilled in the art with no reasonable expectation of success that replacing the fused, interacting protein with a fused, interacting nucleic acid would facilitate protein complementation and reconstitute enzyme activity. For example, nucleic acids are highly negatively charged molecules due to their phosphate backbone, which is in contrast with proteins which have varying charges depending on amino acid composition. A fused, interacting nucleic acid which is highly negatively charged could cause the nucleic acid/protein complex to aggregate or cause the polypeptide portion to not properly fold and be incapable of restoring catalytic activity. Further, even if the polypeptide portions fold properly, the fused, interacting nucleic acid itself could inhibit reassembly of the catalytic activity by blocking the ability of the enzyme fragments to interact. This unpredictability is independent of the further unpredictability associated with ability of the probe portion in the present invention to bind to the target analyte and position the polypeptide fragments to catalyze the reassembly of activity.

The Examiner states that column 29, line 61 to column 30, line 25 and column 31, lines 2-20 of Michnick et al. disclose an embodiment wherein complementation molecules are brought together by attached nucleic acid-binding proteins which simultaneously bind to nearby regions of a target nucleic acid. Office Action at page 8. Applicants respectfully submit Michnick et al. is directed to a method of detecting protein interactions, not a target analyte. Example 4 at column 29, line 61 – column 30, line 28 is directed to the detection of protein interactions of molecules linked to the split enzyme mediated by a third entity, such as DNA, RNA, or small molecules, not to the detection of a target analyte, much less a nucleic acid target analyte. The use of fused, interacting proteins to detect protein interactions mediated by a third entity such as a nucleic acid is not interchangeable with a method of using a nucleic acid probe to detect a nucleic acid analyte. In addition, the use of a nucleic acid probe allows the detection of any nucleic acid rather than, as in Michnick et al., the use of a protein probe which requires the protein binding site to be present in the nucleic acid and thereby limits the number of naturally occurring nucleic acid molecules which could even be detected. Therefore, one skilled in the art would not be led to reconstitute the catalytic

activity of a split enzyme by the use of a nucleic acid probe binding to any nucleic acid target analyte, nor is there provided a requisite basis for a reasonable basis of success.

Based on the multiple layers of complexity and limited predictability regarding the substitution of a protein component for a nucleic acid component in the present detection system, a person skilled in the art would have no reasonable expectation of success in arriving at the claimed invention in view of Landegren et al. and Michnick et al.

Based on the totality of the facts, the claimed invention provides highly sensitive methods to accurately detect nucleic acids in intact cells, and a person skilled in the art would not have been motivated to combine Landegren et al. and Michnick et al. or have a reasonable likelihood of successful in achieving the claimed methods in view of Landegren et al. and Michnick et al.

*Singer et al. and van Dongen et al.*

Singer et al. and van Dongen et al. do not cure the deficiencies of Landegren et al. and Michnick et al. Singer et al. and van Dongen et al. discuss nucleic acid hybridization assays using, for example, a chromophore or fluorochrome. Column 1, lines 63-64 and column 4, lines 4-7, respectively. Note that the chromophore or fluorochrome in Singer et al. and van Dongen et al. are intact, complete molecules competent of producing a signal without complementation. The use of an intact chromophore or fluorochrome results in reduced detection sensitivity as both probes bound to a target analyte and probes unbound to the target analyte produce signal. The present invention as claimed provides new and improved methods of detecting nucleic acids of interest which solve the problem in prior technology such as Singer et al. and van Dongen et al. related to lack of sensitive due to high background signal and inability to detect low abundance nucleic acids.

Landegren et al. in view of Michnick et al., and further in view of Singer et al. or van Dongen et al. do not teach or suggest the claimed invention.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claims 1-3, 5-12, 14, 16-17, 19, and 25-26 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S.

6,270,964), and further in view of Singer et al. (U.S. 5,728,527) or van Dongen et al. (U.S. 6,730,474).

*II. Claim 4*

Claim 4 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964), further in view of Sodroski et al. (U.S. 5,654,195), and further in view of Singer et al. (U.S. 5,728,527) or van Dongen et al. (U.S. 6,730,474). Applicants respectfully traverse.

The Examiner argues that one of ordinary skill in the art would have been motivated to substitute polypeptides which together form a discontinuous epitope recognized by an antibody for the enzyme-forming polypeptides in the method of Landegren et al. as modified by Michnick et al. in view of Sodroski et al. Office Action at page 10.

Applicants respectfully disagree. Landegren et al., Michnick et al., Singer et al., and van Dongen et al. are discussed above. Sodroski et al. does not cure the deficiencies of Landegren et al., Michnick et al., Singer et al., and van Dongen et al. Further, Sodroski teaches antibodies against discontinuous epitopes on a *single* molecule, i.e., a HIV-1 protein (column 12, lines 41-43), but does not specifically teach a method to detect discontinuous epitopes from two separate proteins or from separate polypeptides which have come together by protein complementation.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claim 18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964), further in view of Sodroski et al. (U.S. 5,654,195), and further in view of Singer et al. (U.S. 5,728,527) or van Dongen et al. (U.S. 6,730,474).

*III. Claim 18*

Claim 18 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964), further in view of Lizardi et al. (U.S. 5,854,033), and further in view of Singer et al. (U.S. 5,728,527) or van Dongen et al. (U.S. 6,730,474). Applicants respectfully traverse.

The Examiner alleges that one of ordinary skill in the art would have been motivated to use rolling circle amplification to provide target nucleic acid in the method of Landegren et al. as modified by Michnick et al. in view of the disclosure of Lizardi et al. Office Action dated December 4, 2008 at page 11.

Applicants respectfully disagree. Landegren et al., Michnick et al., Singer et al., and van Dongen et al. are discussed above. Lizardi et al. does not cure the deficiencies of Landegren et al., Michnick et al., Singer et al., and van Dongen et al.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claim 18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964), further in view of Lizardi et al. (U.S. 5,854,033), and further in view of Singer et al. (U.S. 5,728,527) or van Dongen et al. (U.S. 6,730,474).

*IV. Claim 20*

Claim 20 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964), further in view of Stefano et al. (U.S. 5,654,195), and further in view of Singer et al. (U.S. 5,728,527) or van Dongen et al. (U.S. 6,730,474). Applicants respectfully traverse.

The Examiner alleges that one of ordinary skill in the art would have been motivated to substitute a triplex detection means for the adjacent binding site means in the method of Landegren et al. as modified by Michnick et al. in view of Stefano et al.

Applicants respectfully disagree. Landegren et al., Michnick et al., Singer et al., and van Dongen et al. are discussed above. Stefano et al. does not cure the deficiencies of Landegren et al., Michnick et al., Singer et al., and van Dongen et al. Applicants note that Stefano et al. teaches a triplex of PNA (peptide nucleic acid) which is a pseudopeptide. A pseudopeptide is not equivalent to duplex nucleic acid probes, as stated in column 2, lines 16-17. Further, the Examiner states that Stefano et al. is cited for the broader teach of nucleic acid detection based on triplex formation; however, nothing in Stefano et al. teach or suggest that triplex formation with two probes binding to

the *same site* is able to reconstitute formation of an assembled complementation complex in the claimed methods. There is no reasonable expectation of success or motivation to combine Landegren et al., Michnick et al., Singer et al., van Dongen et al, and Stefano et al. to arrive at the methods of claim 20.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claim 20 under 35 U.S.C. § 103(a) over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964), further in view of Stefano et al. (U.S. 5,654,195), and further in view of Singer et al. (U.S. 5,728,527) or van Dongen et al. (U.S. 6,730,474).

*V. Claims 21-23 and 27-28*

Claims 21-23 and 27-28 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964). Applicants respectfully traverse.

The Examiner alleges that one skilled in the art would have been motivated to substitute polypeptides which together form a complementation complex of Michnick et al. for the complementary nucleic acids in the methods of Landegren et al. Office Action at page 4.

Applicants respectfully disagree. Landegren et al. and Michnick et al. are discussed above. Applicants submit that the kits of claims 21-23 and 27-28 are nonobvious in view of Landegren et al. in view of Michnick et al.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claims 21-23 and 27-28 under 35 U.S.C. § 103(a) over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964).

*VI. Claim 24*

Claim 24 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964) and further in view of Sodroski et al. (U.S. 5,654,195). Applicants respectfully traverse.

The Examiner alleges that one skilled in the art would have been motivated to substitute polypeptides which together form a discontinuous epitope recognized by an antibody, for the

enzyme-forming polypeptides in the method/kit of Landegren et al. as modified of Michnick et al. Office Action at page 5.

Applicants respectfully disagree. Landegren et al., Michnick et al., and Sodroski et al. are discussed above. Applicants submit that the kit of claim 24 is nonobvious in view of Landegren et al. in view of Michnick et al. and further in view of Sodroski et al.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claim 24 under 35 U.S.C. § 103(a) over Landegren et al. (U.S. 2002/0064779) in view of Michnick et al. (U.S. 6,270,964) and further in view of Sodroski et al. (U.S. 5,654,195).

## CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 632852000100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 4, 2009

Respectfully submitted,

Electronic signature: / Stephanie Yonker /
Stephanie Yonker
Registration No.: 58,528
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-4227